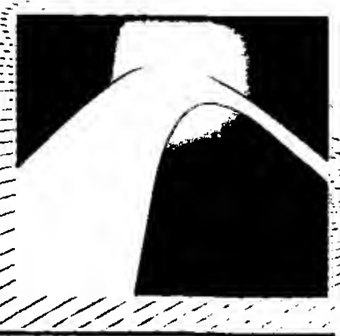
Koninkrijk der Nederlanden

OCTROOICENTRUM NEDERLAND



Hierbij wordt verklaard, dat in Nederland op 10 mei 2004 onder nummer 1026154,
ten name van:
Jacob KOREVAAR
te Haarlem
een aanvrage om octrooi werd ingediend voor:
"Inrichting en werkwijze om een fluïdum aan een zoogdier toe te dienen",
onder inroeping van een recht van voorrang, gebaseerd op de in Nederland op
24 februari 2004 onder nummer 1025556 ingediende aanvrage om octrooi, en
dat de hieraan gehechte stukken overeenstemmen met de oorspronkelijk ingediende stukken.

Rijswijk, 22 maart 2007.
De Directeur van Octrooicentrum Nederland,
voor deze,

D.H. de Haas

Abstract

The invention relates to a device and a method for the administration of fluids, such as fluids containing an active substance, to a mammal, via the pulmonary route. According to the invention the device for administration of an aerosol to a mammal comprises:
aerosol means for creating an aerosol in the device,
an opening for releasing the aerosol from the device, wherein
the device is provided with control means, for adding energy to or removing energy from the aerosol in order to thereby control the particle size of the aerosol, prior to releasing the aerosol from the opening.
With the device and method according to the invention the administration of an (active) substance via the pulmonary route can be controlled with a much better accuracy, then would be possible with devices or methods according to the prior art.

Device and method for administration of a fluid to a mammal

The present invention relates to a device and a method for administration of an aerosol to a mammal, the device comprising:

- aerosol means for creating an aerosol in the device,
- an opening for releasing the aerosol from the device.

There are five common routes for administration of (active) substances to the body:

1. across mucosal membranes (nasal, ophthalmic, or sublingual delivery),
2. by injection or infusion (including intramuscular, intravascular, or subcutaneous delivery),
3. through the digestive tract (oral or gastrointestinal delivery),
4. through the skin (transdermal delivery), and
5. through the respiratory tract (pulmonary delivery or inhalation).

Pulmonary administered substances can have different aggregate conditions: gas, liquid or solid. Pulmonary administration can be intended to have both a medical and non-medical effect. Inhalation of substances can be done both through the nose and the mouth. Substances for inhalation can be targeted at the body's systemic circulation system, but likewise they can be aimed to have an effect from the point of administration onwards.– i.e. from the mouth/nose through to the deep lung.

Traditional drug delivery methods – except injection and infusion – are used primarily with small molecules, such as individual peptides. Pulmonary delivery is already in use for a variety of small-molecule drugs, mainly to treat respiratory disorders. Drugs with respiratory applications include anti-inflammatory agents, bronchodilators and protease inhibitors. Yet, the deep lung is also a favourable environment for non-invasive delivery and absorption of large molecules – as the alveoli (deep lung) provide an extensive air-blood interface allowing large-molecule proteins and peptides access to the body's systemic circulation. Therefore pulmonary drug delivery has the potential to be a much more effective route of administration of macromolecules, with a relatively higher bioavailability than with any other route except injection or infusion. However, the development of deep lung delivery systems could increase patient acceptance and improve compliance – as an alternative to the invasiveness of injection.

Inhaled liquid and solid substances eventually deposit, while gaseous substances are taken up through exchange. However, the inhaled substances may be partly exhaled. The deposition area of the body comprises the mouth, the nose, the throat, the airway, the bronchi and the alveoli. The desired location for deposition is primarily determined by the intended effect and the yield of the substance to be inhaled.

Gas exchange occurs primarily in the alveoli. In that case the gas is absorbed into the blood. Solids and liquids can likewise be absorbed into the blood.

For pulmonary administration of liquid and solid substances to the body, in most cases a device is used that produces a fine particle mist. When administering liquids the mist consists of small moisture particles (aerosol) and in the case of solids a fine powder mist is obtained. The inhalation of dispersed drugs is most common in the treatment of pulmonary conditions such as asthma, bronchitis, and emphysema. Drug delivery products with respiratory applications include Dry-Powder Inhalers (DPIs), Metered-Dose Inhalers (MDIs), and nebulizers.

During production and inhalation of a fine particle mist, lack of uniformity is an important problem. The particles differ in diameter and usually the particle size distribution is unsymmetrical. As a result the fine particle mist has a mean and median size, a standard deviation and a certain bandwidth. The larger the bandwidth, the wider is the deposition area of the inhaled substances.

Note: mathematically, the most abundant particle size in a mist equals the mean and the median size only in the case of a symmetrical distribution. Some medical specialists however consider the most abundant particle size in a produced mist as the median size even in the case of an unsymmetrical distribution. In this document the mathematical median is used rather than the most abundant particle size.

Investigations have revealed that the particle size of a fine particle mist strongly influences its deposition behaviour. This implies that as a result of size, an inhaled particle will deposit in a certain location in the trajectory from mouth/nose to the alveoli. In addition the respiratory level (the flow containing the inhaled fine particle mist in litres per minute) affects the

deposition behaviour. A relatively low respiratory level requires the inhaled particles to be relatively small for optimum deposition in the lower airways and deep lung. An increased respiratory effort can partly prevent premature deposition of relatively large inhaled particles – e.g. in the upper airways.

Users of pulmonary delivery devices have their own respiratory behaviour. Furthermore the conditions of the trajectory mouth/nose to alveoli may strongly vary between users. As a result the deposition behaviour of a substance to be inhaled is difficult to predict. Since the mean particle size of an aerosol to be inhaled is often larger or smaller than the optimum size for the particular respiratory level of a user, the presumed deposition behaviour strongly deviates from the actual deposition pattern. For that reason control of the deposition behaviour is an important issue.

The use of existing pulmonary delivery devices for administering a substance in many cases results in inefficient deposition. Existing inhalation drug delivery systems typically also deliver only a fraction of the drug to the deep lung, as most of the drug is lost in the delivery device or in the patient's mouth and throat. Due to the fact that the patient must co-ordinate the breathing manoeuvre with aerosol delivery, Dry-Powder Inhalers and MDI's also fail to provide the deep-lung dosage reproducibility that is necessary for many systemic applications. In addition, therapeutically valuable macromolecules currently cannot be formulated for use in MDI systems, as macromolecule drugs are denatured by the MDI formulating ingredients. A similar problem is associated with drug nebulization, which also tends to inactivate therapeutic macromolecules. In addition, dry-powder systems do not provide the protection needed for the long-term stability of macromolecule formulations. Therefore existing inhalation drug delivery systems such as dry-powder inhalers, metered-dose inhalers (MDI's), and nebulizers are used primarily to deliver drugs to the upper airways of the lung for the treatment of lung diseases.

A known device for administration of pharmaceutical preparations according to the introduction is a dry-powder inhaler (DPI). Dry-powder inhalers are breath-actuated devices that use the siphon effect generated by the patient's inhaled air stream to deliver and disperse a drug in fine powder form into the lungs. When using the dry-powder inhalers a person can breathe in and thereby create a fine power mist, which is administered to the lungs. The mist is generated and administered without the need of

strict breathing co-ordination that is required for the proper use of a MDI (see below). Dry-powder inhalers do not need propellants and preservatives.

A disadvantage of the use of a dry-powder inhaler is the fact that the functional effectiveness of the apparatus depends on the patient's ability to generate adequate respiratory effort and airflow turbulence for disrupting larger powder formations and producing an aerosol of drug particles of respirable size. Thereby, the siphon that is used to create the mist does not contribute to the reproducibility of the required dose. In addition, dry-powder systems do not provide the protection needed for the long-term stability of macromolecule formulations. Therefore the existing dry-powder inhalers are used primarily to deliver drugs to the upper airways of the lung for the treatment of long diseases.

Despite some functional limitations of DPIs and their higher average price compared to equivalent MDIs, the relative usage of DPIs in the management of COPD patients has expanded rapidly in the past three to four years. Currently, several design versions of DPIs are available in the U.S. including GlaxoSmithKline's Accuhaler™, Diskhaler™, Rotahaler™, Spinhaler™, and Tubuhaler™.

The Accuhaler™ contains a foil strip of 60 blisters, each containing a unit dose of the drug with a lactose carrier. The Diskhaler™ contains a coarse net that creates turbulence to de-aggregate the drug particles. The drug is contained within four or eight foil-blistered discs, allowing multidose administration. The Rotahaler™ is a single-dose system that uses a coarse net to de-aggregate the drug particles and requires reloading with a capsule containing an appropriate drug dose. The Spinhaler™ is a single-dose system that uses a rotor mechanism to expel the drug and requires reloading with a capsule containing an appropriate drug dose. The capsules required in the Rotahaler™ and the Spinhaler™ may be susceptible to moisture. The Turbuhaler™ releases a unit volume of drug into 2 high-resistance, spiral channels, which create a vortex and optimise particle size when the patient's inspiratory flow rate is greater than 30L/min. This multidose device indicates when 20 doses are left and does not use a propellant, the lack of which reduces coughing and mutes the taste of the drug.

AstraZeneca offers the Pulmicort Tubuhaler™ and the Symbicort Turbuhaler™, a new dry-powder inhaler that offers adjustable dosing, which enables doctors to tailor a patient's treatment with a single inhaler.

The Symbicort Turbuhaler™ is a combination of the budesonide, corticosteroid, and the rapid-onset, long-acting bronchodilator formoterol in a dry-powder inhaler.

Another known device that is used to administer fluid to a mammal is a so-called metered-dose inhaler (MDI). This type of device is the most widely used drug-delivery device for inhalation drug therapy of COPD.

Metered-dose inhalers use propellants from a pressurised container to deposit micronized particles of a drug into the airways. The propellant is pressurised and mixed with a fluid containing a drug. When releasing the mixture from the pressurised container an aerosol is formed with micronized particles of typically $1-3$ μm. During administration, the particles will travel into the airways as far as halfway the bronchi. Thereafter the propellant will evaporate, leaving the remaining particles in the lung and allowing them to travel deeper into the lung system. The fact that the mixture of propellant and active particles is feed into the lungs and the fact that the propellant has to evaporate initially in order to allow the particle to move on, creates a time delay when administering the drug to a patient.

In the MDI-system the container canister is sealed with a special metering valve designed to release a predetermined volume of drug-containing aerosol in each actuation. Within the MDI, the drug is suspended in a propellant with added lubricants and surfactants. Various devices can deliver up to 400 doses; the container's lifetime depends on the volume of drug delivered per actuation.

An advantage of an MDI system, when compared with the above-mentioned DPI, is the fact that the systems are resistant to moisture and relatively cheap.
An important disadvantage of the MDI-system is that fact that an exact co-ordination is required in the actuation of the device with inhalation. The deposit of active particles will depend on the co-ordination of the created aerosol and the inhalation of a patient.
Lung deposition from a MDI is further affected by the position of the inhaler in relation to the lips, the lung volume at inhalation, the inhaled flow rate and the breath holding of a user after the inhalation (typically for 10 seconds).

Other problems include the lack of a dose counter and the "cold Freon" effect, in which the patient stops inhalation as the aerosol reaches the throat. The low temperature of the mixture

entering the body and the reflex of the user not wanting to inhale the cold fluid causes this effect.

In order to improve the operability of the MDI-systems, a Breath-actuated MDI was developed to improve the efficiency of drug delivery in patients who have difficulty in co-ordinating their breathing efforts with the working cycle of conventional pressurised MDI. Breath-actuated MDI combine conventional MDI with a spring-driven activation mechanism, which requires priming and is triggered by the patient inhaling at flow rates of 30L/min or more.
This requirement limits the usability of the systems, since many patients, such as COPD patients, will not be able to generate the required flow rate.

Breath-actuated MDI do not require the co-ordination that is necessary with conventional MDI; however, some patients are startled by the release of the spring, which causes glottic closure. This problem may be overcome by using some of the newer MDI, which feature special, quieter activation mechanisms. The clinical efficacy of a breath-actuated MDI system is equivalent to that of a correctly used conventional MDI system in asthmatics and COPD patients.

A further attempt to improve the use of the MDI's is the use of plastic spacers or holding chambers in order to overcome poor co-ordination of actuation by the patient and the cold Freon effect. Spacers are attached to the exhaust opening and are available in different sizes. Small-volume spacers are available as integral or detachable components of MDIs. Large-volume spacers, which are sold separately and typically replaced every 6 to 12 months, allow the velocity of the aerosol to decrease before inhalation, allowing time for propellant evaporation and reduction in droplet diameter to less than 5μm, thereby increasing pulmonary drug deposition. With large-volume spacers, high-velocity particles are deflected into the inhaled stream, increasing the efficiency of drug delivery.

An important drawback of the use of spacers, however, is that repeated actuations of the MDI and delayed inhalation from the spacer is associated with up to 50% loss in drug delivery to the lung. These effects result from both static electricity and the fact that the half-life of the drug aerosol within the spacer is only 10 seconds. Weekly washing, with the spacer left to stand after rinsing, reduces the level of static electricity.

Due to concerns regarding the impact of chlorofluorocarbon (CFCs) on the earth's ozone layer, the Montreal Protocol—a legally binding international agreement—obliges all parties to reduce, then eliminate, all production and use of ozone-depleting substances, particularly CFCs, which have been used as aerosol propellants. As a result, the new CFC-free DPIs are propelled by the more environmentally friendly hydrofluoroalkanes (HFAs). To date, only a few CFC-free MDI models (relying on HFA-based propellants) have been launched in the U.S. However, CFC-free devices are expected to take the place of conventional MDIs in the coming years.

Other companies offering MDIs in the U.S. include Nektar TherapeuticsTM and SkyePharmaTM.

A third type of device for the administration of fluids according to the introduction is a nebulizer. This device produces aerosols by either passing compressed air rapidly through a liquid or by vibrating a liquid at a high frequency using ultrasound. Both of these methods provide an effective mist for delivering medications. Pneumatic units are considered superior from the standpoint of depth of delivery, as they produce a finer mist that travels deeper into the lungs, although ultrasonic units are much quieter to operate and do not require a heater.

Despite the fact that the compressor or ultrasound unit represents an equipment investment of at least approximately $125, the actual nebulizer is nearly always purchased as a disposable unit to reduce the risk of cross infection. The exception is with patients who are receiving home healthcare; in some of these cases, the patient may prefer to rely on reusable or semi-disposable nebulizers to reduce costs. Treatment nebulizers are small reservoir, handheld updraft devices used for intermittent delivery of medications. They are used primarily in hospitals and for home-based immobilised COPD patients. Medication nebulizers are indicated for the delivery of "custom" doses of bronchodilators, corticosteroids, and mucolytics.

AstraZeneca's Pulmicort RespulesTM is the first nebulized corticosteroid in the U.S. for use by children as young as 12. After the premixed dose of liquid medicine in the respule is opened, the medicine is poured into a nebulizer, which uses a compressor to aerosolise liquid medication, then delivers it via a facemask or mouthpiece. The NIH recognises the nebulizer as an effective delivery method for infants and young children. Nebulizers are now

widely used in the U.S. to deliver nonsteroidal asthma medications. The Pulmicort RespulesTM is a preventive measure, not a quick-relief treatment, and is not used to treat asthma attacks.

Beside the apparent disadvantage of the price of the device, an important disadvantage of the present nebulizers is the fact that these devices deliver only a fraction of the drug to the deep lung, as most of the drug is lost in the delivery device or in the patient's mouth and throat.

Investigations have furthermore revealed that both deposition and uptake of an inhaled substance influence the effect and the response time of the administered substance. Therefore the deposition behaviour of the substance to be inhaled must be considered when prescribing a dose and determining the ideal moment of intake. Inefficient deposition - as a result of failure to do so - is an obstacle for pharmaceutical and biomedical companies to ensure optimum use of their substances through inhalation.

For an optimum deposition effect, the deposition behaviour of the substance to be inhaled must be controlled in every possible way. As an example, it may be important to improve the uniformity of the produced mist. In addition, it may be desirable to modify the mean particle size as required, e.g. to adjust it to the respiratory profiles of a generic group of users or that of an individual user.

With reference to the above an object of the present invention is to improve the administration of a fluid to a mammal. This object is in a first aspect achieved in that the invention provides a device for administration of an aerosol to a mammal comprising:

- aerosol means for creating an aerosol in the device,
- an opening for releasing the aerosol from the device, wherein
- the device is provided with control means, for adding energy to or removing energy from the aerosol in order to thereby control the particle size of the aerosol, prior to releasing the aerosol from the opening.

In a second aspect the invention relates to a method for administration of an aerosol to a mammal, comprising the steps of:

- creating an aerosol, and
- administration of the aerosol to the mammal, wherein the method comprises the step of:

- manipulating the aerosol by adding or removing energy from the aerosol in order to thereby controlling the uniformity and/or the mean particle size of the aerosol of the particles of the aerosol, prior to releasing the aerosol to the mammal in order to deliver the (active) substance at a predetermined deposition area in the respiratory tract and/or the lung system of the mammal.

According to the invention it is preferred that the method comprises the step of:

- adding an active substance to the aerosol, prior to releasing the aerosol to the mammal, in order to use the aerosol as a carrier to administer the substance to a mammal.

An affect of this measure is the ability to control the conditions of a mixture before inhalation in order to positively influence the deposition behaviour of the substance to be inhaled.

The present invention provides a device and a method for the administration of an aerosol to the lungs of a mammal. It is important for the present development that the aerosol's state and condition can be controlled, as a result of which the aerosol can be adjusted as required prior to the inhalation thereof.

In the present text the wording 'mammal' is used. Mammal in the text refers to any human being or animal having a lung system.

In the present invention the wording 'fluid' is used. This refers to any liquid, gas, aerosol or the like.

In the present text the wording "aerosol" is used. This refers to a mixture of a gas and moisture particles in that gas, including the moisture in a gas state in said gas.

In the above text wording is used such as 'the human body', 'a patient' etc. It is to be understood that the disclosed device and method can be used with the same advantages and effect in the administration of fluids to mammals.

In the process of administration of an aerosol according to the present development, the following steps can be identified:

Step 1: In a first process step it is to be determined what the preferred state and condition of the aerosol used for administering an (active) substance should be during administration thereof. The preferred conditions of the aerosol mainly depend on the (active) substance to be delivered and the preferred deposition effect for that (active) substance. Furthermore, the state and condition of the user can play a role.

Step 2: In a second process step an aerosol is created.

Step 3: In a third process step the aerosol is manipulated to adjust the state and condition of the created aerosol in order to e.g. control the uniformity and mean particle size of the aerosol, dependent on the preferred state and condition as established in Step 1.

Step 4: In a fourth step an (active) substance is added to the aerosol.

Step 5: In a fifth step the aerosol is administered to a mammal.

According to a preferred device and method all of the five steps mentioned are required in order to prepare and administer an (active) substance to a mammal. Depending on the (active) substance to be delivered however, it is possible to administer an (active) substance not requiring the use of Step 4. Furthermore, the sequence of steps may be varied as appropriate, where obviously any manipulation of any aerosol requires the prior creation of that aerosol and likewise any manipulation occurs prior to administration. In addition, the preferred state and condition of the aerosol will de determined prior to finishing the manipulation thereof. It is possible to execute some of the steps simultaneously.

Here below, the requirements and the details of the Steps 2, 3, 4 and 5 will be discussed in detail.

The present invention provides a device and a method comprising with means to produce a mist of small moisture particles for inhalation. It is possible to introduce such a mist from outside the device rather than producing the mist inside the device. The means for producing a mist of small moisture particles is referred to as the "aerosol source".

The aerosol source used to generate this mist may produce moisture particles containing an active substance, such as medication. It is also possible, that these moisture particles only contain inactive carriers, such as water. A combination of active and inactive substances is also possible. Furthermore the aerosol source can be breath-actuated, or use can be made of a partial or complete support mechanism that is manually or automatically operated. Different aerosol sources could be used simultaneously in the system.

The mean particle size and the uniformity of a produced mist of moisture particles, vary between aerosol sources. The mean particle size may range from e.g. sub-nano up to sub-millimetre in diameter. Depending on the intended deposition effect of the substance to be inhaled and the ability to control state and condition of the aerosol, an inhalation delivery device may be equipped with a specific aerosol source. This way the mist of moisture particles may have a state and condition as required for the following manipulation process.

Various methods and devices are available for creating a mist of moisture particles. Therefore an inhalation delivery device may use an aerosol source based on existing technology. It is also possible that eventually a newly developed technology is used. Below, four examples for creating an aerosol are described.

It is possible to produce an aerosol by either passing compressed gas rapidly through a liquid or by vibrating a liquid at a high frequency using ultrasound. Both methods will provide a mist, which is capable of delivering a medication to the lungs of a mammal. Pneumatic units provide a fine mist, with a relatively small particle size.

The use of a mist generator will produce an aerosol with a limited uniformity. That means that the particle size will vary and that the bandwidth and standard deviation are considerable.

As an option the aerosol could be formed directly from a liquid containing an active substance. As described below, preferably the (active) substance to be administered is added to the aerosol in a separate step. A combination of both is also possible.

A preferred option to produce an aerosol is to use a fuel cell. According to this method hydrogen and oxygen are fed to a traditional fuel cell, creating heat, electricity and molecular water (water in gas phase).

The use of a fuel cell has many advantages. The first advantage is the fact that the creation of the aerosol starts with the creation of a gas containing moisture at molecular level. Therefore this particular method offers the possibility to create an aerosol with a much smaller (mean) particle size than with any other existing method. In addition, aerosols formed from said gas will have an extremely uniform particle size. Both bandwidth and standard deviation of the aerosol will be minimal. This uniformity will have the effect that the handling and the further processing of the aerosol in the device can be predicted and repeated with even greater accuracy than with any other existing method.

A further advantage of the use of a fuel cell is the fact that the generation of the gas will produce electricity, which can be used for the control systems in the device.

Since the aerosol is used for e.g. drug delivery purposes, a further advantage is that the created water will be sterile. In addition, a filter may be used to purify the flow – as most delivery devices make use of ambient air. This filter can remove particles, bacteria and/or viruses from the flow.

In order to create an aerosol from the formed gaseous water, the gas will be transported to a condensation chamber.

An additional advantage is the fact that a condensation chamber is a relatively simple technical device. It suffices to have an enclosed space with a controlled temperature. A condensation chamber is in its construction a much simpler device then for instance an evaporation chamber.

The use of a catalytic process is similar to the use of a fuel cell as described above. The major difference is the fact that only thermal energy is produced; no electrical energy. A catalytic process may use a liquid fuel, such as methanol instead of hydrogen, wherein an (active) substance may be dissolved or where the (active) substance is coupled with the fuel. During the catalytic conversion the (active) substance is liberated in a predetermined form. In this way the addition of the (active) substance is integrated with the creation of an aerosol.

It is possible to produce an aerosol by pumping a liquid through a heated capillary. The capillary is heated to a constant and relatively high temperature. The liquid entering the capillary is volatilised by the application of heat creating a vapour pressure and causing the vapour to exit the capillary as a vapour jet. The exiting jet entrains the ambient air and rapidly cools, achieving the supersaturated conditions necessary for homogeneous nucleation within a few millimetres of the capillary jet. Aerosol formation is complete within a few centimetres of the tip, yielding a low velocity jet of fine aerosol particles at near ambient temperature.

As an option the aerosol could be formed directly from a liquid containing the (active) substance to be inhaled. Care should be taken that the (active) substance to be inhaled is able to resist the temperature needed to volatilise the liquid in the capillary. Therefore, the use of this method is limited. As described in paragraph 7, preferably the active substance is added to the aerosol in a separate step. A combination of both is also possible.

In step 1 the desired state and condition of the aerosol used for the administration of an (active) substance to be inhaled is determined, based on the intended deposition effect of this (active) substance. In step 2 an aerosol is created or introduced. Subsequently in step 3 this starting aerosol is manipulated and controlled, such that a change of state and condition of the aerosol – used for the administration of the (active) substance – positively influences the deposition behaviour of the (active) substance to be inhaled. To that effect Inhaleness has developed an inhalation device and method that can manipulate and control the mean and/or median particle size of an aerosol, the bandwidth and standard deviation thereof, prior to the administration thereof. For the repeatability of the administration of an (active) substance using an aerosol, it is also important to be able to manipulate or control the state and condition of the aerosol.

The proposed method distinguishes a starting aerosol (input) from a desired aerosol (output). Depending on the (active) substance to be delivered and its desired deposition effect, the requirements for controlling and manipulating the state and condition of the produced aerosol are more or less stringent.

According to the present invention controlling both uniformity and main particle size of an aerosol, starts with the choice of an appropriate method for creating the aerosol. Depending

on the method used for the production thereof, the aerosol will have a typical mean particle size, median, standard deviation and bandwidth.

In order to ensure that a starting aerosol leaves the inhalation device in a desired state and condition, the aerosol is manipulated and controlled prior to administration. To that effect energy is added to or extracted from the aerosol, with the objective to convert moisture from a molecular level (gas) to a liquid form or vice versa. As a result the mean particle size, median, standard deviation and bandwidth of the aerosol change.

In order to add energy to or extract energy from an aerosol, both temperature and pressure can be used as parameters. It is also possible to use a combination of both parameters. In order to avoid the use of pressurised chambers– in a simple embodiment – it is preferred to use temperature only. In order to add energy to or extract energy from an aerosol, the temperature of the aerosol must either increase or decrease.

For the sake of convenience the starting aerosol is assumed to contain moisture particles, i.e. moisture in liquid form. The moisture particles act as condensation nuclei. Since smaller particles exhibit a higher area to volume ratio than larger particles, the smaller particles cool and evaporate at a higher rate than larger particles. This implies that any moisture present at a molecular level (gas) will condensate at the surface of the smaller particles rather than at the surface of the larger particles. As a result the smaller particles will grow at a higher rate than the larger particles– until an equilibrium condition is reached. Consequently the mutual difference in particle size decreases and thus the standard deviation and bandwidth of the aerosol. In addition the mean particle size and median shift to a higher value and the symmetry of the particle size distribution is improved.

During a condensation process energy is extracted from the aerosol causing the mean particle size to increase. During an evaporation process energy is added to the aerosol and the mean particle size decreases. Contrary to condensation, where the number of moisture particles is practically unchanged, during evaporation the number of moisture particles decreases. This time the uniformity improves as well. The smaller particles evaporate at a higher rate than the larger ones. As a result the bandwidth decreases, the standard deviation gets smaller and the particle size distribution becomes more symmetrical.

By extracting energy from the aerosol in a controlled way or similarly adding it, the uniformity of the aerosol particles and the increase or decrease of the mean particle size of the aerosol can be controlled. In this respect controlled means that a specific amount of energy is extracted from the aerosol or added thereto, with the objective to convert a specific quantity of moisture from a molecular level (gas) to a liquid form or vice versa. As a result a certain bandwidth, standard deviation, median, symmetry in mean particle size can be realised.

In order to determine the specific amount of energy to be added or extracted, the heat capacity of the gas and the moisture present in the aerosol is evaluated. The physical values of the heat capacity are subsequently plotted against the quantity of moisture to be converted from a molecular level (gas) to liquid form or vice versa. As a result the amount of energy that must be extracted from the aerosol or added thereto, in order to realise a desired conversion of moisture from the one to the other aggregate condition. When this specific amount of energy is then actually extracted from the starting aerosol or added thereto, the state and condition of the aerosol change as desired. This is referred to as a regulated condensation process and/or evaporation process.

In order to determine the specific amount of energy that must be added to a starting aerosol or extracted from it, it is also possible to exclusively consider the heat capacity of the moisture that is present in the aerosol and neglect the heat capacity of the gas that is present in the aerosol. The result does not necessarily deviate very much from the intention since the yield difference is relatively small. The heat capacity of a gas is after all orders of magnitude smaller than that of a liquid.

On the other hand it is possible to use the evaporation rate or evaporation yield as reference for certain applications in addition to the heat capacity. This is done to enable a more accurate manipulation and control of the starting aerosol. For that reason it may be more appropriate to refer to the heat properties of the gas and liquid present in the aerosol.

When the parameter temperature is used to extract a specific amount of energy from an aerosol or add it thereto, the corresponding temperature gradient must be determined. The required temperature gradient is determined on the basis of the heat capacity of the gas and moisture that is present in the aerosol and the specific amount of energy that must be extracted from the aerosol or added thereto. As a result of the temperature decrease or

increase of the aerosol, the desired quantity of moisture will be converted from one aggregate condition to the other. Obviously it is possible to determine the temperature gradient exclusively from the heat capacity of the moisture that is present in the aerosol and not that of the gas present.

At the start of this paragraph it is indicated, that on the basis of the intended deposition effect of a (active) substance to be inhaled, a desired state and condition can be determined for the aerosol that is used to administer the (active) substance to the body. Subsequently the starting aerosol can be manipulated and controlled, to bring the actual state and condition of the aerosol to better correspondence with the desired state and condition, with the objective to positively influence the deposition behaviour of the (active) substance to be added. As a result the deposition behaviour of the administered substance shows a better fit of with the intended deposition effect thereof. Subsequently it is indicated, that Inhaleness manipulates and controls the state and condition of an aerosol by extracting an amount of energy from the aerosol or adding it thereto. As a result a quantity of moisture is converted from the one to the other aggregate condition, thus changing the state and condition of the aerosol that is used to administer an (active) substance to be inhaled. The degree to which the state and condition of a starting aerosol is modified differs between applications and/or users. Furthermore the degree of accuracy with which this is done may differ.

During manipulation of the state and condition of an aerosol, the ideal situation is reached in case of 100% yield. That means all energy that is extracted from an aerosol or added thereto, is used for the conversion of moisture from the one to the other aggregate condition. Unfortunately, in practice losses will always occur, even though additional precautions may be taken to reach an optimum yield. The higher the yield, the more accurate the state and condition of an aerosol can be controlled.

For example in an inhalation device proposed by Inhaleness, an aerosol source is present that produces a starting aerosol. The aerosol source uses existing techniques and produces an unsaturated aerosol. The starting aerosol is subsequently manipulated and controlled, such that the aerosol can leave the inhalation device in a desired state and condition. As mentioned, in order to manipulate the state and condition of the aerosol, a certain amount of energy is extracted from the aerosol or added thereto of with the objective to convert a quantity of moisture from the one to the other aggregate condition.

In this example a desired state and condition of the aerosol is assumed that requires an increase in mean particle size. This implies that moisture at a molecular level (gas) must be converted to moisture in liquid form. To this effect energy must be extracted from the aerosol, using the parameter temperature. In that case the aerosol must be subjected to a certain temperature decrease, in order to convert a specific quantity of moisture from a molecular level (gas) to moisture in liquid form.

The problem is however, that the starting aerosol is in an unsaturated condition. As a result a temperature difference exists that must be bridged in prior to reaching a relative humidity of 100% in the aerosol. Only after that, will a further decrease in temperature convert a quantity of moisture at a molecular level (gas) to moisture in liquid form. This implies that the amount of extracted energy in first instance is obtained from a temperature decrease of the aerosol down to the condensation point.

If the starting aerosol prior to manipulation has a relative humidity of e.g. 90%, then the yield is only reduced to a limited extent. This is caused by the relatively small temperature jump that must be realised, prior to reaching the condensation point. If the relative humidity is e.g. 40%, the yield reduction is obviously larger. In that case a relatively large temperature jump is required prior to reaching the condensation point.

Even if energy is added to the starting aerosol instead of extracted thereof, the yield is reduced. When the relative humidity decreases during evaporation of an aerosol the yield goes down. When adding energy to an unsaturated aerosol the yield is lower than when adding energy to a saturated aerosol.

It is obvious that a reduced yield does not contribute to the manipulation and control of the state and condition of an aerosol. In case of a reduced yield, more energy must be extracted from the aerosol or added thereto in order to realise the desired conversion of moisture from the one aggregate condition to the other. The additional energy required for that, is difficult to determine when e.g. the dew point and the relative humidity of a starting aerosol are unknown. In the existing inhalation devices these parameters are unknown. For that reason the inhalation device and method proposed by Inhaleness may use measuring systems that enable a more accurate manipulation and control of the aerosol.

The quantity of gas entering the inhalation device and used to produce a starting aerosol can for instance be measured. In addition the temperature of this gas can be measured. The relative humidity of this gas can also be measured. Furthermore the quantity of moisture that is added to this gas during production of the starting aerosol can be determined. It is also possible to measure the temperature of the nebulized liquid. By plotting the heat properties of the moisture and gas, that are present in the aerosol, against one or several of the parameters previously mentioned, the determination of the proper amount of energy required to realise a desired change of state and condition of the aerosol is facilitated. To the extent that more of the parameters are known, the manipulation and control can take place with a higher accuracy.

An alternative solution is to validate the process of making the starting aerosol. That means from clinical or laboratory investigations the amount of energy actually added to the starting aerosol or extracted thereof, in order to realise the desired conversion of moisture and the desired change of state and condition, is known. The validation is used for making adjustments to the theoretical equations that are applied for manipulation and control.

It is also possible to replace the aerosol source that is used, by an aerosol source that produces a starting aerosol with a relative humidity of 100%. That means, the starting aerosol has reached the condensation point. When subsequently energy is extracted from the aerosol or added thereto, the yield will be optimum.

When it is not possible to apply an aerosol source that produces an aerosol with a relative humidity of 100%, or when for instance too few parameters of the starting aerosol are known, it can be desirable to deploy a condenser in order to bring the starting aerosol in a saturated condition. Because the aerosol leaves the condenser with a known temperature and a relative humidity of 100%, the manipulation and control of the state and condition of the aerosol is facilitated. Thus an optimum starting situation has been created. It is also possible to realise the desired state and condition of an aerosol directly with the aid of the condenser, such that administration thereof to the body can be the next step.

The modification of the mean particle size and/or the uniformity is not equally important for all applications. The manipulation and control of an aerosol may for instance be used to

change an aerosol from an unsaturated condition to a saturated condition. It is also possible that the control means are used to increase or rather decrease the relative humidity of an aerosol. Medications are known for instance that act better at a high than at a low relative humidity and vice versa. The manipulation and control of an aerosol can of course be done with the intention to modify the mean particle size and/or the uniformity of the aerosol.

Through the conversion of moisture from the one to the other aggregate condition, a change in the uniformity and the mean particle size is realised. When it is important that this modification results in a specific final value for the uniformity and/or mean particle size, then the uniformity and the mean particle size of the starting aerosol must be known. Based on these starting values the quantity of moisture that must be converted from the one to the other aggregate condition can be determined.

In order to learn the mean particle size of a starting aerosol, prior validation and/or measurement of parameters can be used. The latter however leads to a more complex inhalation device, whereas for many applications this is not necessary. It is possible to solely consider a state and condition that is expected beforehand. That means, in the past a validation of the production process of the aerosol has taken place and on that basis the uniformity and/or de mean particle size of the starting aerosol can be predicted. In both situations, the starting value is known. Subsequently the quantity of moisture that must be converted from the one to the other aggregate condition can be determined. Next, based on the heat properties of the gas and moisture that are present in the aerosol, the specific amount of energy can then be determined that is required to realise the desired change of state and condition of the aerosol.

The intended state and condition of the aerosol leaving the inhalation device, to an extent can be a fixed value. That means, a certain substance with an intended deposition effect is administered and on that basis a certain state and condition of the aerosol are desired for the administration of that substance. Additional factors that may have a variable influence on the desired state and condition thereof during the process of making, manipulating and administrating the aerosol are not taken into account.

Considering the desired state and condition of an aerosol as a fixed value, implies a generalising effect. For some applications this mode of operation will suffice. When however

for a certain application for instance the respiratory level of the individual user must be taken into account, this cannot be done. Due to the intended deposition effect of a substance to be inhaled, the respiratory level during inhalation demands a specific state and condition of the aerosol carrying the (active) substance to be inhaled. Therefore the desired state and condition of the aerosol can differ per user. Furthermore the desired state and condition of the aerosol may vary during the use of the inhalation device.

The inhalation device en method according to the invention is able to measure in real time in order to determine the desired state and condition of an aerosol. It is possible to measure for instance the respiratory level of the user and use that to control the manipulation of the aerosol. As a result the mean particle size of the aerosol can be adjusted to an optimum value, corresponding with the intended deposition effect of the substance to be inhaled that is carried by the aerosol and the respiratory level of the user.

Previously reference has been made to the parameters pressure and/or temperature that can be used to extract an amount of energy from the aerosol or to add it thereto, with the objective to change the state and condition of the aerosol. There is another parameter however that can be used to this effect, which is the relative humidity. Here below an explanation is given with an example.

An inhalation device proposed by Inhaleness administers an aerosol to the user based on the flow-through principle. That means, a certain quantity of gas is introduced to the system. This can be done by using the respiration of the user and/or a supporting mechanism, for instance a ventilator. A number of moisture particles is added to the flowing gas with the aid of an aerosol source. As a result an aerosol is created. Subsequently the aerosol flows through the inhalation device and the state and condition of the aerosol are manipulated prior to leaving the inhalation device. To that effect energy is extracted from the aerosol or added thereto, for which the parameters pressure and/or temperature can be used. Preferably the parameter temperature is used. Thus no pressure chambers are required and the total volume of the flowing aerosol remains equal, since no gas or other aerosol is added.

It is possible however, that the state and condition of the aerosol are manipulated by adding another gas or another aerosol thereto. This way energy can also be extracted from the aerosol or added thereto. When a gas with a lower relative humidity than that of the aerosol is added,

the aerosol will extract energy from the gas. As a result energy is indirectly added to the starting aerosol. When a gas with a higher relative humidity than that of the aerosol is added, the aerosol delivers energy to the gas. This means that energy is indirectly extracted from the aerosol. By controlling this process, it is possible to control the state and condition of the aerosol. Controlling this process means, taking the relative humidity and the volume into account of both the starting aerosol and the gas or aerosol added thereto. By adjusting these parameters relative to each other, while taking into account the heat properties of the used gas and/or moisture, the state and condition of the starting aerosol can be manipulated.

In summary, manipulation and control of the state and condition of a starting aerosol can take place with the aid of a controlled condensation process and/or evaporation process. To that effect the starting aerosol is cooled, heated, diluted or varied in pressure. The previously mentioned control means can be deployed separately or in combination. Thus it is possible for instance to cool initially, heat next and subsequently dilute. Another sequence or combination is also possible.

At the time the preferred state and condition of the aerosol leaving the device are calculated, it is preferably taken into account that upon leaving the device and entering the body of the mammal, the state and condition of the aerosol will change again and the uniformity and mean particle with it.

The additional advantage of bringing a starting aerosol to a saturated condition by applying a temperature gradient is, that the temperature of this saturated aerosol is known. Suppose the temperature of the saturated aerosol is 50 degrees centigrade. When the saturated aerosol is subsequently administered to a human, the aerosol will decrease in temperature, until the moment that the Carina is reached. That location in the body has a constant temperature and a relative humidity of 100%. Since the temperature decrease of the saturated aerosol is known, the quantity of moisture at a molecular level (gas) that is converted in the trajectory to moisture in liquid form is known. From this information the growth of the mean particle size, prior to reaching the Carina can be deducted.

To prevent the aerosols from increasing in size as a result of continued condensation, we add unsaturated gas, e.g. ambient air, preferably with the same temperature as that of the saturated mixture leaving the condenser. As a result, we bring down the degree of saturation of the

mixture causing the aerosol to partly evaporate. By adjusting the ratio of unsaturated gas added and the mixture itself, the aerosol leaving the inhalation device will have a predetermined state and condition allowing the fine moisture particles to reach their appropriate size on their way from the device to the desired target deposition area.

The process steps of making an aerosol, the manipulation thereof, the addition of an (active) substance thereto and the administration thereof can be integrated. This can be done in various ways. Here below two examples are given.

In an inhalation device according to the invention, a catalytic process is used as the aerosol source. This aerosol source produces a gas containing molecules of moisture. The (active) substance desired to be added, may be present in the produced gas. This gas is subsequently introduced to a condenser. The gas becomes saturated, condenses and leaves the condenser with a certain temperature in order to be administered.

An alternative possibility is an inhalation device wherein a fuel cell is used as the aerosol source. The fuel cell produces a gas containing water at a molecular level. The substance desired to be added is no part of the produced gas. The gas is led through a condenser prior to adding the substance to be added. The produced gas leaves the condenser as an aerosol with a relative humidity of 100%. Subsequently the substance to be added to the aerosol can be added. In order to prevent the added substance to act as condensation nuclei, it may be decided to initially dry the aerosol by dilution prior to adding the substance to be added .

Once the saturated aerosol leaves the condensation chamber, the aerosol may be diluted by means of a gas, such as ambient air. The dilution of the aerosol means that the condensation process will be inverted. The dilution of the aerosol will decrease the dew point thereof. The dilution of the aerosol, for instance, is achieved by using a gas with essentially the same temperature as the saturated aerosol.

The particle size of the aerosol reaching the exit of the device for administration of the aerosol, irrespective of the question whether an active substance is added to the aerosol or not, mainly depends on the particle size of the aerosol when leaving the condensation chamber in combination with the dilution of the aerosol downstream of the condensation chamber.

The combination of condensation and dilution may be used to fine-tune the aerosol in order to obtain an aerosol with the preferred particle size.

In order to manipulate and control the state and condition of the aerosol, the aerosol may be fed to a condensation chamber. The aerosol entering the condenser has a specific state and condition. Usually the aerosol source governs the state and condition of the aerosol. It is possible however that the state and condition of the aerosol are adjusted prior to entering the condenser. To that effect the inhalation device may be provided with the appropriate means.

Thus it is possible that the aerosol entering the condenser is filtered in order to remove for instance fine dust particles or that some of the moisture particles that are present in the aerosol are captured. Likewise it is possible to partition the aerosol produced by the aerosol source over several condensers. Furthermore several aerosol mixtures may be combined, after which this combined mixture flows through a condenser or is partitioned over several condensers. In addition several aerosol mixtures can for instance subsequently flow through a condenser or of separately or jointly enter several condensers. It is also possible that prior to or upon entering the condenser a substance is added to the aerosol. Furthermore it is possible that the introduced aerosol is changed in volume prior to entering the condenser; for instance by separation.

The condensation chamber will have the form of an enclosed space, preferably with a first open end to receive the aerosol in the condensation chamber and a second open end to release the aerosol. Because of these features the condensation chamber can be used as a flow-through condensation facility, with a minimal obstruction of the flow of the aerosol towards the exit of the administration device. As a result of resistance in the condenser, the flow rate of the aerosol leaving the condenser is probably lower than it is when entering the condenser. It is also possible to deliberately increase that flow rate with the aid of supporting means. Use can be made of an adjustable resistance.

In the condensation chamber means are provided to cool the aerosol flowing by. As a result the temperature of the aerosol gradually decreases, resulting in the aerosol leaving the condenser with a lower temperature than it had upon entering. In the condenser cooling can be effected from the outside inwards– that means the walls are cooler than the entering aerosol. It is preferred however to cool from the inside outwards– in that case the walls of the condenser

have a temperature that is higher than or equal to the temperature of the aerosol entering and/or continuing through the condenser, while the aerosol flows along and eventually through a cooling element that is placed inside the condensation chamber. This set up has the advantage that no condensation occurs on de walls. A combination of both ways is also possible however.

As mentioned, the aerosol flows along – and preferably through - a cooling element that is placed inside the condensation chamber. As a result the aerosol flowing by will decrease in temperature. The cooling element can be placed symmetrically in the channel, however this is not a prerequisite. If desired, the walls of the condenser may consist of a material that discourages condensation or may be provided with such a material. In addition measures can be taken to reduce the resistance, such as smooth (plastic) walls– eventually provided with such a material, for instance a coating. The cooling element, along which the aerosol flows, can also exist of material that discourages condensation or be provided with such a material. Condensation on the cooling element is not absolutely required, since a starting aerosol already contains condensation nuclei in the from of small moisture particles.

The temperature may be set to ensure that the aerosol will be fully saturated at the time of leaving the condensation chamber. Although in theory the total quantity of moisture in the aerosol leaving the condenser should equal the quantity of moisture that the aerosol contained upon entering, in practice the quantity of moisture in the aerosol leaving the condenser will probably be lower as a result of 'losses'. Moisture can for instance be removed by means provided to that effect. This moisture may be transferred to a storage tank in the device or may be discharged outside the device – eventually this moisture may be added to the aerosol source and/or an aerosol entering the condenser. Measures can be taken to capture the moisture particles present in the condenser with a certain size, for instance by moisture separation. Due to a low flow rate it may occur that moisture particles with a certain size are no longer carried and 'drop out' of the aerosol.

In order to retrieve the condensation energy, which is released in the condensation chamber a Peltier-element may be used. The energy that can be retrieved by means of said Peltier-element may be used for control systems in the device.

After leaving the condensation chamber the aerosol can in principle be administered to a mammal. As described below, it is also possible to add an active substance to the aerosol prior to that.

The device according to the invention is adapted to create, manipulate and administer an aerosol, the aerosol being a carrier for the delivery of an active substance, such as a drug to a mammal.

There are several options to ensure that the aerosol contains an active substance. A first option is to produce an aerosol from a liquid containing the active substance. According to the present invention an active substance may be present in the liquid used to produce the aerosol. However, in a preferred embodiment of the device the active substance is added to the aerosol in a separate step. Thereafter the combination of the aerosol and the active substance is administered to a mammal.

Below three different techniques for adding the active substance to an aerosol will be described. The techniques relate to the addition of an active substance in the form of a gas, liquid or solid to the aerosol.

It is to be understood that the methods can be multiplied or can be used in parallel. That means for instance, that a first and a second active substance, in the form of a liquid and an active substance in the form of a gas may be added to the same aerosol.

In case an active substance is added in the form of a medical gas, the doses will be relatively small. In case a large amount of gas is to be delivered to a patient, it will be more practical to use a respiration device.

The active gas will be present in the device in a canister. The addition of the gas to the aerosol can take place by opening a valve, which closes the exit of the canister.

In practice, it is very advantageous to use an aerosol for the administration of a limited amount of gas.

In the first place the flow of the aerosol will provide the necessary energy for the transport of the gas to the lung system of a mammal.

The aerosol and the particles in the aerosol will also ensure good mixing of the limited amount of gas with a reasonable amount of ambient air in order to be able to administer the gas in a diluted form.

Since the presence of the aerosol will ensure good mixing, the gas in the canister can have a high concentration of active substances, without running the risk of overdosing a certain area in the body of the mammal during the administering of the active substance.

A further advantage is the fact that the aerosol, for instance in the form of a water vapour, will also provide the necessary moisture to moisturise the lung system of a mammal during the administration of the gas.

There are several ways to ensure the mixing of an active substance in the form of a liquid with an aerosol.

I: According to a first method the liquid containing the active substance is pumped through a membrane. The membrane is provided with apertures with a size typically in the range of 0,3-0,7 μ

II: According to a second method, the liquid containing the active substance is put under pressure and allowed to adjoin a membrane provided with apertures. Since the flow of the aerosol adjoins the opposite side of the membrane, the pressurised liquid is allowed to evaporate and as a result a vapour containing the active substance is added to the aerosol. The particle size of the particles entering the aerosol flow will depend on the size of the apertures in the membrane. The particle size is relatively small, allowing the particles to evaporate in the aerosol flow.
Because of the good mixing that can be obtained between the aerosol and the active substance added to the aerosol, the active substance can be added with a high concentration, in small quantities. The advantage thereof is that a small reservoir containing the active substance will suffice for a large number of doses. This is possible because of the fact that according to the present development the active substance is not dissolved in its carrier when provided in the administration device, but is added to a separate carrier in the device itself.

Due to the fact that the gas is relatively dry, the passing gas (flow through principle) is 'hungry' for moisture. This moisture is formed at the surface of the membrane. At that membrane surface the liquid medicine is coming through

III: According to a third method the active substance is dissolved in a propellant, such as CO_2. The propellant and the active substance are contained in a canister, closed by means of a valve. Upon opening the valve the propellant and the active substance are released and enter the flow of the aerosol. The propellant will evaporate and the active substance will be carried towards its destination by means of the aerosol.

The active substance is in the production phase mixed, coupled or bound chemically to an evaporating substance. This evaporating substance will allow the active substance to be released from the canister. The evaporating substance will not be used as a carrier to transport and deliver the active substance. The evaporation of the substance will allow the active substance to be adhered to or mixed with the aerosol. The aerosol will be the carrier transporting the active substance to the preferred deposition area.

The evaporating substance will typically evaporate in order to limit the distance of travel of the combination of active substance and evaporating substance to less then 50 mm.

In case the propellant is CO_2, the evaporated propellant can be inhaled by a mammal without creating any health risk for the mammal.

In case an active substance in the form of solid is to be added to an aerosol, two cases have to be distinguished.

A first group of solid active substances will dissolve in a liquid. Those substances can be added to the aerosol in a way similar to the addition of a liquid to the aerosol.

A second group of solid active substances will not dissolve in a liquid. This second group of solid active substances can be added to the aerosol in the form of a powder. Since the particles of the active substance are added to an aerosol, which is not 100% saturated, the particles will not initiate further condensation of the aerosol. The powder will be taken up by the particles

in the aerosol and carried by the aerosol. The particle size of the powder will determine the growth of the resulting particle size of the combination of aerosol and powder particles.

In order to avoid clustering of the powder particles during addition to the aerosol, the particles may be added to the aerosol, using an electrical device in order to provide the particles with a certain electrical charge.

The level of saturation will be 100% at the level of the carina.
The fact that according to the present development solid active substances can be added to a mammal, using an aerosol has the advantage that the inhalation of an aerosol containing a dry powder will be much more comfortable, then the inhalation of a dry powder, for instance using a gas flow as a carrier.

Once the aerosol has reached the outlet of the administration device, it is ready to be administered to a mammal. Since the aerosol is manipulated to have the preferred particle size for the active substance to be delivered, the predictability of the deposition of the active substance is greatly improved when compared to prior art devices and methods.

The predictability of the deposition will allow a much better control of the active substance administered to a user.

There are several options for the administration of the aerosol to the mammal. The system can be breath-actuated, meaning that the intake of the aerosol will be dependent on the respiratory effort of the mammal. The system can also work with a breath support, meaning that the device will help the mammal with the intake of the flow.
The device according to the present development can also be used in line.
It may be used in combination with a mask or a mouthpiece.

According to the present development the administration of the aerosol can be monitored and managed using a real time control system. This control system requires the use of sensors, control mechanism and process means to fine-tune administration of the active substance depending on the specific administration conditions to a preset value for optimal delivery.

The control system must be adapted to fine-tune the amount of active substance to be administered and must be able to time the addition of the active substance to the aerosol, in a breath cycle.

The flow can be measured directly by means of a sensor or can be deducted using a combination of a flow obstruction and a pressure sensor.

The present invention can be used as a breath operated system. That means a user has to provide a minimum respiratory effort to initiate a flow through the device towards the mouth.

A breath-actuated system may very well be equipped with a fuel cell for the production of the aerosol. In this case the user generates a flow, which will be led over a membrane in the fuel cell. The aerosol will then travel via the condensation area towards the exit of the device. Prior to leaving the device, an active substance can be added to the aerosol. In this case, the control of the flow through the device is mainly dependent on the momentary respiratory effort of the user.

In case a user is not able to generate any flow, or is only capable of generating a limited flow through the system, additional means may be provided in order to improve the flow through the system towards the exit thereof. These additional means may have the form of an appropriate fan or ventilator.

In order to closely monitor the flow in the device-mammal interface, the device is preferably provided with a flow meter. This flow meter is preferably connected to a control mechanism, capable of controlling the additional flow that is to be generated by the ventilator.

During the transfer of the aerosol to the mammal, the lung system of the mammal will be gradually filled with the incoming aerosol. Since the active substance can be added to the aerosol in a separate step, it is possible to select the time of addition of the substance to the aerosol. That means in case the active substance is meant to enter the deep lungs, the active substance is added to the aerosol at the start of a breath cycle. The active substance will be carried to the essentially empty lungs and therefore reach a deeper level of the lungs then in case the active substance was added to the aerosol at the end of a breath cycle. The later the

moment the active substance is added to the aerosol, the closer to the mouth the deposition area of the active substance in the mammal will be.

In order to be able to time the moment of addition of the active substance to the aerosol, the system is preferably provided with a combination of a flow meter and a control mechanism, to monitor the flow towards the mammal and to be able to choose the preferred moment for adding the active substance to the flow.

Since according to the present development the active substance is added to the aerosol in a separate step, the addition of active substance may take place at chosen intervals not necessarily coinciding with every breath cycle. This enables the device to adjust the addition of the active substance to the preferences of a specific user.

Thereto the device is preferably provided with means for instance to set a maximum amount of active substances to be administered to a user, per time unit. Moreover, the device then preferably comprises means to measure and store the amount of active substances added to the aerosol, per time unit. Depending on the use of the device by a specific user, the device can then add active substance to the aerosol in order to ensure that the user receives the required dose, without the risk of overdosing.

At the moment the aerosol is administered to the user, the aerosol can be diluted. This dilution may take place by adding ambient air to the flow to be administered to the user.

The following five steps have been identified in the method of administration of an active substance to a mammal:

Step 1: Determination of the preferred particle size of the aerosol during administration thereof, depending on the purpose of the active substance;

Step 2: Creation of an aerosol;

Step 3: Manipulation of the aerosol to control the particle size of the particles in the aerosol;

Step 4: Addition of an active substance to the aerosol; and

Step 5: Administration of the aerosol to a mammal.

It is to be understood that the different steps 1-5 are interrelated.

For example, in case the amount of aerosol created in a breath-actuated system decreases, due to a decrease in the respiratory effort of the user, the parameters for the manipulation of the aerosol must be amended in order to ensure an optimal particle size of the aerosol.

Here below the parameters that are of interest for each of the five steps and the interrelation of each of the steps is discussed in more detail.

The preferred particle size of the aerosol depends on the preferred deposition area of an active substance in the lung system of a mammal. The preferred particle size also depends on the actual flow of aerosol in a breath cycle.
The actual particle size of the aerosol and the flow of aerosol in one breath cycle in combination with the timing of addition of the active substance to the aerosol in that breath cycle, determine the resulting deposition area of the active substance in the lung system.

I: The preferred deposition area of the active substance depends on the following parameters:

- The active substance to be delivered to the mammal,
- The area in the lung system to be reached and/or treated with the active substance,
- In case of a malfunction in the body of the mammal, the specific malfunction that is to be treated,
- The amount of active substance to be administered to the mammal,
- The age of the mammal.

Most of the indicated parameters can be pre-programmed in a device to administer the active substance. It is possible to provide the device with process means, such as a computer, which are able to receive and store the specific parameters for a specific use of the device.
It is also possible to add information on the preferred deposition area, and thus the preferred particle size of the aerosol, on the packaging of the active substance. This information may be supplied in the form of a Bar Code. Thus when a user inserts a capsule or similar packaging with active substance in the delivery device, the device is automatically provided with information on the operational details for the administration of the active substance in the capsule.

II: The actual flow through a device depends on the respiratory effort of a user, in case a breath operated system is used. In a device provided with means such as a ventilator to assist

the flow, the actual flow depends both on the user and the additional flow generated by the system. The actual flow is preferably measured upon delivery of the aerosol to the mammal in the fifth step of the process. This information is preferably fed back to the control means in order to (re)calculate the preferred particle size of the aerosol.

In practise, the device can be provided with control means to calculate a preferred particle size for the aerosol based on an estimated flow. The measurement of the actual flow can then be used to adjust the control of the particle size in the device. As an option a minimum number of breath cycles may initially be measured and the actual flow may be used to fine tune the control of the particle size, prior to the addition of any active substance to the aerosol in the Fourth Step, thus ensuring that the active substance actually reaches the preferred deposition area.

This means that depending after a measurement of the flow, the manipulation of the particle size in the device can be changed in order to adapt the particle size to this flow level. Alternatively, the flow can be regulated by using additional flow means in order to obtain the preferred flow level, without the need of changing the particle size of the aerosol. A combination of the two (changing both particle size and flow) could also be used.

The required particle size and the required accuracy relating to the bandwidth and standard deviation of the particle size in the aerosol are the main criteria in selecting a technique for the creation of the aerosol.

After the creation of the aerosol the aerosol is manipulated in order to control the particle size of the aerosol. The preferred particle size - as determined in the First Step of the process - determines the degree to which the parameters regulating the manipulation of the aerosol are varied in order to obtain that preferred particle size.
As previously described, according to the present development, the manipulation of the aerosol takes place in two steps. In the first step the aerosol is saturated. In the second step the aerosol is diluted with a gas, such as ambient air.

The addition of the active substance is depends on the following parameters:

- The active substance to be delivered to the mammal,
- The area in the lung system to be reached and/or treated with the active substance,

- In case of a malfunctioning in the body of the mammal, the specific malfunctioning that is to be treated with the medication,
- The amount of active substance to be administered to the mammal,
- The age of the mammal,
- The psychic condition of the mammal.

The addition of the active substance will be interrelated with the actual flow in the device. The addition of the active substance is preferably regulated depending on the frequency of the use of the device by a user.

As described above, the device may be provided with means to set a maximum amount of active substances to be administered to a user per time unit. Moreover, the device preferably comprises means to measure and store the amount of active substances added to the aerosol, per time unit. Depending on the use of the device by a specific user, the device can then add active substances to the aerosol in order to ensure that the user receives the required dose, without the risk of overdosing.

An important effect is the timing of the addition during a breath cycle. The later the moment the active substance is added to the aerosol, the closer to the mouth the deposition area of the active substance in the mammal will be.

A further aspect of the addition of active substances and the control thereof is that the device may be used as a placebo. The user may use at a frequency he prefers, while the device regulates the actual intake of a maximum amount of active substance per time unit.

In a similar way, the device may be provided with alarm means to inform a user, in case he has not received sufficient active substance per time unit.

The administration of the aerosol will take place from the outlet of the device. The amount of aerosol and the flow administered from that outlet depend on the respiratory effort of the user or alternatively on the additional flow generated in the device or on a combination of the two.

The actual flow from the device towards the patient is preferably monitored in order to control the process steps 1-4, as described above and to thereby control the deposition of the active substance in the lung system of the user.

The systems for monitoring the flow from the device to the user may comprise flow sensors. The control system and the sensors can get their energy for operation thereof from a battery in the system or alternatively directly from a fuel cell, in case the latter is present in the device for the production of an aerosol.

An example of the device is shown in the accompanying drawings, wherein:

Fig. 1 shows schematically the production of a vapour by means of a fuel cell;

Fig. 2 shows a fuel cell stack;

Fig. 3 shows schematically an embodiment of an inhaler with a fuel cell for creating a vapour, enclosed in a housing;

Fig. 4 shows the inhaler according to Fig.3 provided with a condenser for creating an aerosol;

Fig. 5 shows the inhaler according to Fig. 4 provided with a dilution chamber, for decreasing the dew point of the aerosol;

Fig. 6 shows the inhaler according to Fig. 5 provided with a mixer, for adding an active substance to the aerosol, and

Fig. 7 shows an embodiment of the condensation chamber in the device.

The development of a new drug involves more than the synthesis of a substance that has a particular effect on the body. The developer must also consider how to transport the drug to the appropriate part of the body and, once there, make it available for use.

With advances in drug development, the way in which a drug is introduced into the body is almost as important as the drug itself. Drug concentration must be maintained at a level that provides maximum therapeutic benefit. The goal of drug administration is the achievement of a desired level of drug concentration and therapeutic effectiveness at the receptor site or site of action.

In a preferred configuration of the invention, a personal inhaler using a fuel cell is shown in FIG 1.

The fuel cell 1 according to Fig. 1 is an electrochemical device that combines hydrogen 2, from a container 2A, and oxygen 3, from a container 3A, to produce water 4, heat 5 and electricity, schematically represented by light bulb 6. Alternatively, the flow of oxygen can be provided by means of ambient air. This is schematically shown in Fig. 3.

As hydrogen 2 flows into the fuel cell's anode 1A and oxygen 3 into the fuel cell's cathode 1B, the fuel cell produces pure water 4 and heat 5. That means that the fuel cell 1 produces a vapour with an elevated temperature.

As shown in Fig. 2, individual fuel cells 1, 11, 21, 31 may be combined into a fuel cell "stack" 10 to increase the total electrical power generated.

The process of generating a warm vapour according to Figs. 1 and 2, according to the invention is entrapped in an inhaler.

Fig. 3 shows the fuel cell 1 positioned inside an inhaler, schematically represented by cylinder 15. The opening 17 for releasing the aerosol is positioned at the right end side of the cylinder 15.

Because of the enclosure 15, the vapour generated in the fuel cell 1 will condense and form a sterile aerosol 16. According to Fig. 3 the required amount of oxygen is provided by the ambient air 18. Alternatively, the oxygen is provided by a container as described with reference to Fig.1.

Upon travelling through the inhaler, from the fuel cell 1 towards the opening 17 the vapour continues to condense causing the particles in the aerosol to increase in size. This is schematically indicated by increasing the size of the represented droplets.
This increase in particle size is undesired, since the particle size of the aerosol determines its stability and the deposition effect.

In order to be able to manipulate the particle size in the aerosol, according to the invention, the inhaler 15 is provided with a temperature-controlled condenser 19. This is shown in Fig. 4. In this condenser 19 a saturated mixture is formed. This enables control over the temperature profile of the aerosol and in particular the particle size of the aerosol.

The presence of the condenser 19, limits the space wherein the vapour is to be created by means of the fuel cell 1. This enclosed space can be referred to as the vapour chamber 14.

In order to further improve the control over the particle size an unsaturated gas, e.g. ambient air, is added to the aerosol in a dilution chamber 20, as shown in Fig. 5. The unsaturated gas is preferably of the same temperature as the saturated fluid leaving the condenser. As a result, the dew point of the mixture is decreased causing the particles in the aerosol to partly evaporate, thereby decreasing the size of the individual particles in the aerosol.

The dew point of the fluid may be further adjusted, to a value below the body temperature. In that case condensation is of the vapour and an increase in particle size is further prevented. In that case the particle size of the aerosol will remain relatively small, even after the aerosol has entered the human cavities. The ratio of unsaturated gas added and the mixture itself determines the new dew point.

The aerosol that leaves the inhaler is merely a carrier for an active substance, such as a drug. The active substances 30 have to be added to the aerosol. This is schematically indicated in Fig. 6. The active substances 30 are mixed with the aerosol in a mixer 35. Although the added substances, such as drugs, will combine with the aerosol, slightly increasing their particle size, the particles in the aerosols that can be created according to the present invention may still have a size no larger than 20 nanometer.

The active substances 30 can be transported to the mixer in the form of a solid, a gas or a substance-aerosol. The aerosol 16 generated in the inhaler will provide the carrier to transport the active substances from the mixer 35 towards the human body.

The aerosol 16 generated inside the inhaler 15 will leave the opening 17 with a predetermined temperature. This temperature can for instance be within the range of 20° - 40°. This temperature level will eliminate the cold Freon effect. This is a huge advantage over the use of standard MDI systems as described in the introduction.

The aerosol 16 that leaves the inhaler 15 at the opening 17, will mainly consist of water droplets. That means that the aerosol, used as the carrier for the active substances is a carrier which does not have any undesired effect on the human body in general or the lungs in

particular. This is a huge advantage over the use of a standard DPI, wherein a dry mist enters the lungs, causing a grating effect and an itchy feeling within the lungs.

The shown embodiment is a breath-actuated device. That means that the user himself will have to generate the required respiratory effort to create a flow from the fuel cell 1, via the condenser 19, dilution chamber 20, mixer 35 towards the opening 17.
The shown embodiment eliminates the need of having a strict breathing co-ordination for administration of the active substances in the lungs.

It is to be understood that an alternative solution wherein the airflow is generated without the respiratory effort of a user is also feasible.

In fig. 7, schematically, a possible embodiment of a condenser 19 is shown. The aerosol 16 will travel from the gas chamber 14, through the condenser 19, towards the exit 17 (not shown) of the device.

The condenser 19 is provided with a heat exchanger 40, preferably comprising a open material, in that the aerosol 16 can flow through the condenser, with a minimal amount of obstruction of the flow by the heat-exchanger.

The heat-exchanger 40 comprises, for instance, a metal wool providing a good heat transfer. The wool for instance comprises copper.

The heat-exchanger 40 is coupled with a heating/cooling device 41, in order to regulate the temperature of the heat-exchanger 40.

In the condenser 19 droplets may be formed. These droplets can be collected and led out of the condenser by means of a guide 42. In case the condenser 19 is operated in conjunction with a device for the generation of an aerosol, which uses a liquid to produce the aerosol from, the fluid collected in guide 42 can be fed back to the device for generation of the aerosol.

The conditions in the condenser 19 will be adapted to have an aerosol 16 at the exit of the condenser which is 100% saturated. The aerosol leaving the condenser will have a stable

physical state, in that there is no more condensation or evaporation of the droplets in the aerosol.

As an additional feature the device according to the present development can be equipped with means to sterilise the device. That means an aerosol is created having a temperature of 100 degrees centigrade, in order to sterilise the device by transporting the aerosol through the device.

With reference to the above it is concluded, that the device and the method as described above provide a cost-effective, clean and sanitary inhalation system. The device is able to proportionally deliver gases, liquids, or solids to the different deposition areas in a human body. The device provides an accurate, controlled and convenient manner of administrating a drug by using an aerosol as a carrier, the aerosol itself comprising a substance, which naturally occurs in the human body. Therefore the aerosol is capable of transporting the administered drug (small and large molecules) to the most effective deposition areas in a human body, without denaturing macromolecules.

The inhaled drug delivery products market is a billion dollar business expected to grow substantially the coming years. The inhaler according to the invention may be developed in clinical, residential and handheld configurations.

The handheld configuration may be provided with a catalytic burner, in particular a fuel cell, which result in a compact and energy self-sufficient personal inhaler. This allows the user to effectively self-administer whatever active substance wherever and whenever with a comfort level that will turn inhalation into recreation.

It is to be understood that any other adequate burner can be used without harming the effectiveness of the device.

Since DPI's – Dry-Powder Inhalers – and MDI's – Metered-Dose Inhalers – are known this inhalation system is referred to as D.E.C.I. or DECI – Deposition Effect Controlled Inhaler.

Claims

1. Device for administration of an aerosol to a mammal comprising:
- aerosol means for creating an aerosol in the device,
- an opening for releasing the aerosol from the device, wherein
- the device is provided with control means, for adding energy to or removing energy from the aerosol in order to thereby control the particle size of the aerosol, prior to releasing the aerosol from the opening.

2. Method for administration of an aerosol to a mammal, comprising the steps of:
- creating an aerosol, and
- administration of the aerosol to the mammal, wherein the method comprises the step of:
- manipulating the aerosol by adding or removing energy from the aerosol in order to thereby controlling the uniformity and/or the mean particle size of the aerosol of the particles of the aerosol, prior to releasing the aerosol to the mammal in order to deliver the (active) substance at a predetermined deposition area in the respiratory tract and/or the lung system of the mammal.

3. Method according to claim 2, wherein the method comprises the step of:
- adding an active substance to the aerosol, prior to releasing the aerosol to the mammal, in order to use the aerosol as a carrier to administer the substance to a mammal.

4. Method according to claim 2 or 3, wherein the method comprises the step of:
- measuring in real time the flow of a first amount of aerosol administered to the mammal,
- using the real time measurements in the device-mammal interface in order to control the manipulation of the aerosol prior to the administration of a second amount of aerosol to the mammal.

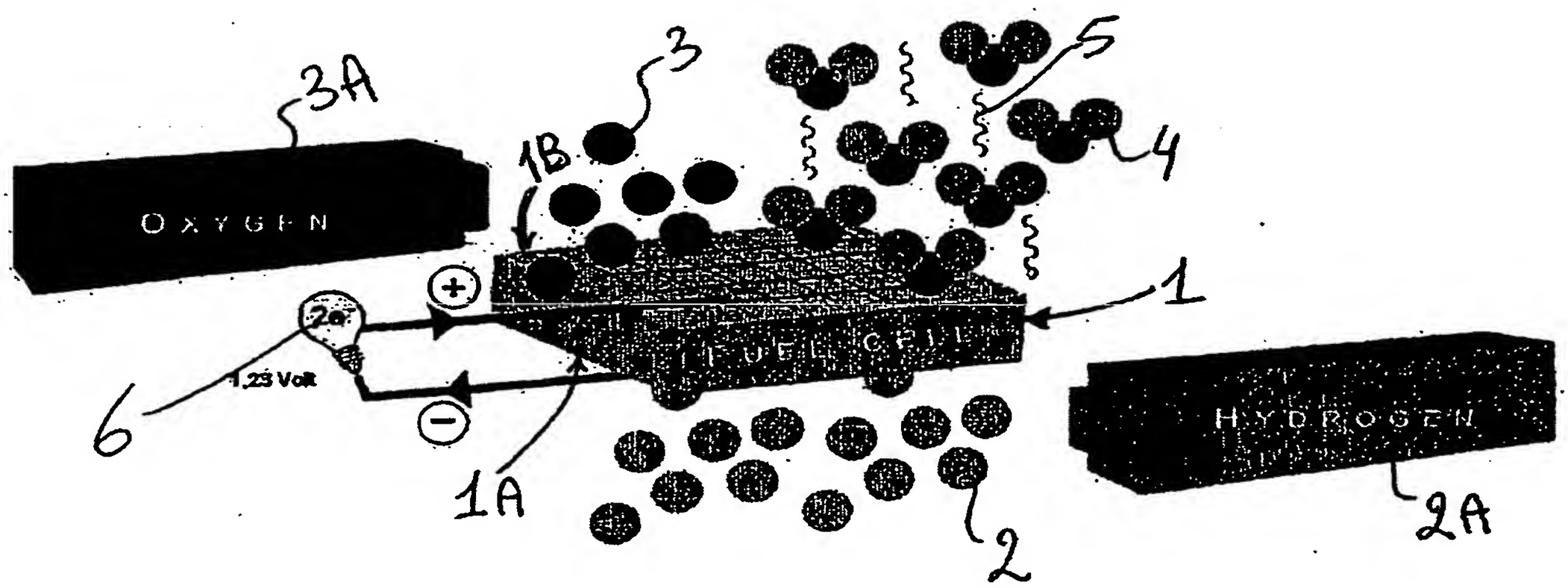


FIG1

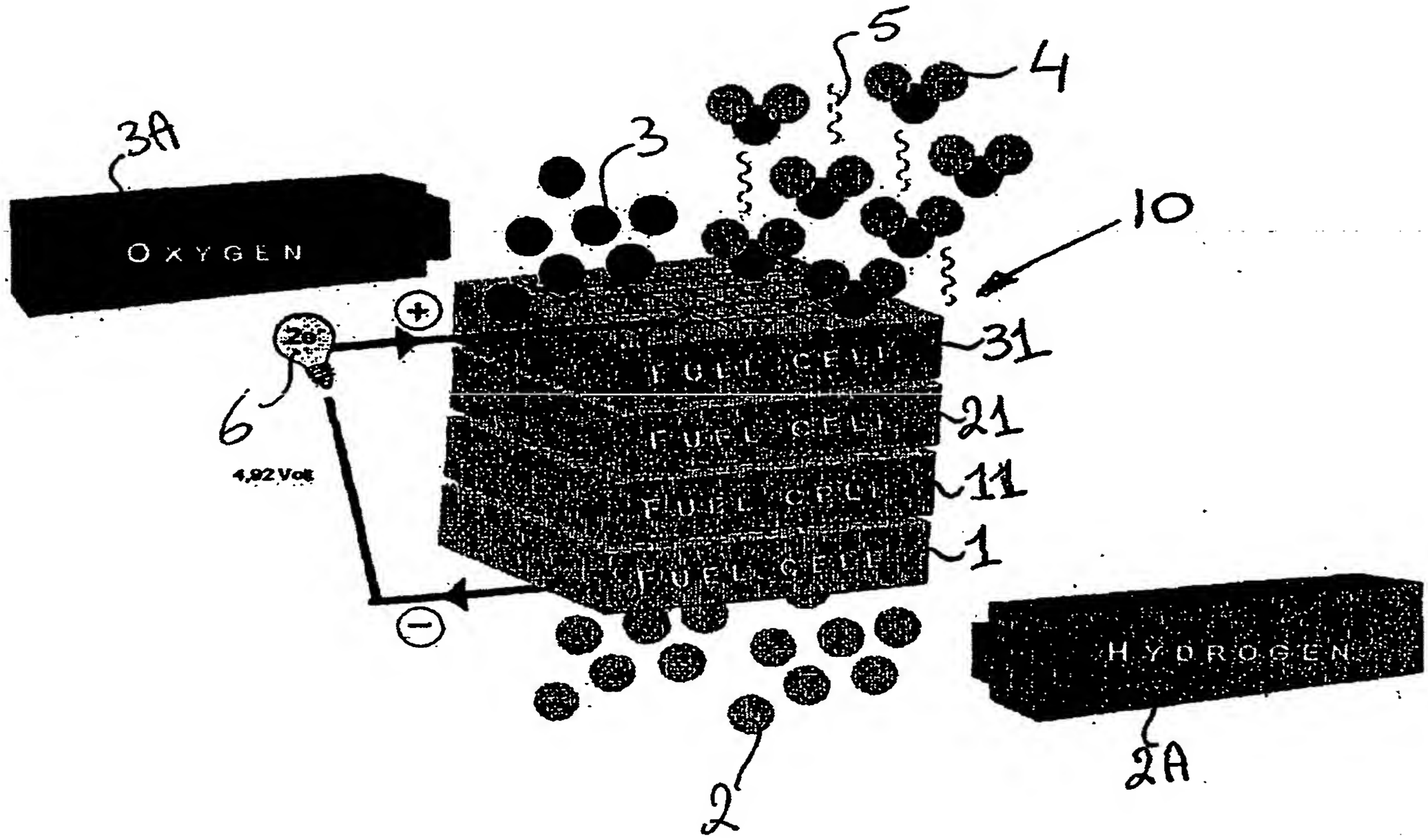

3A
OXYGEN
3
5
4
10
31
21
11
1
6
20
4,92 Volt
+
−
FUEL CELL
FUEL CELL
FUEL CELL
FUEL CELL
HYDROGEN
2
2A

FIG 2

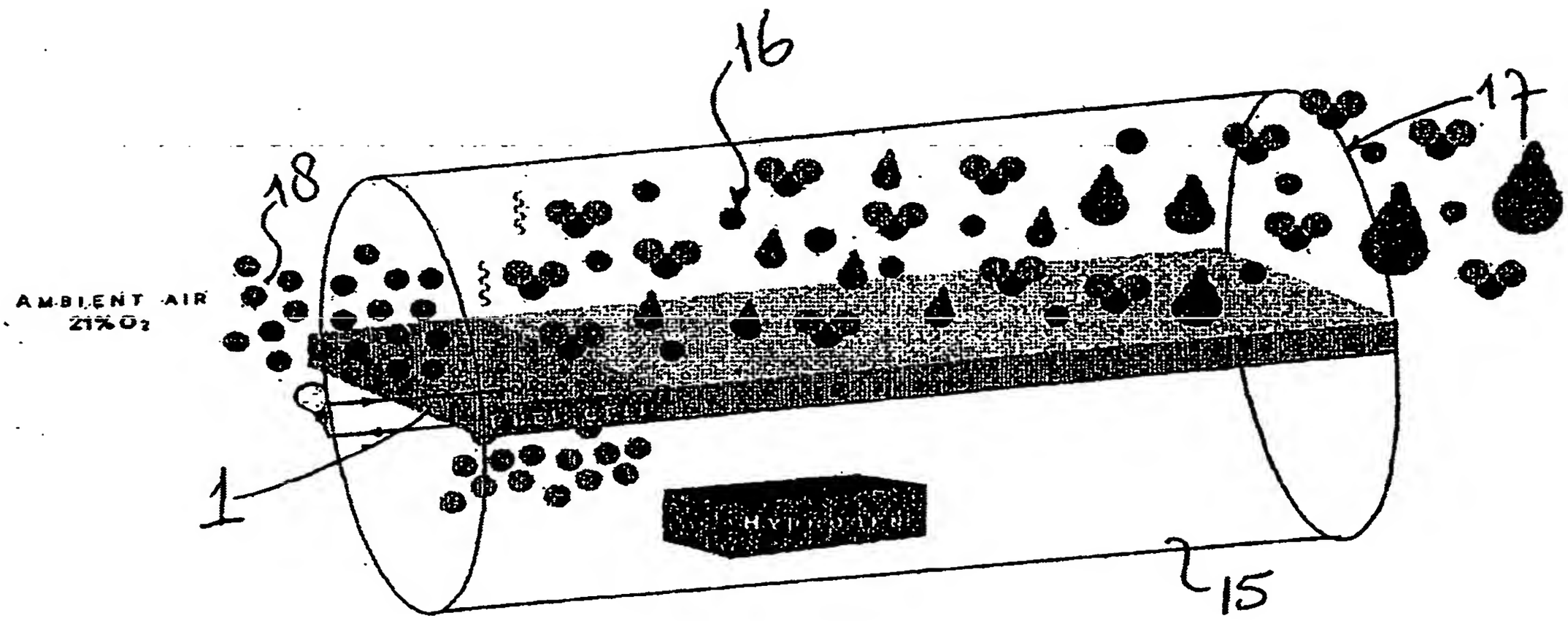


FIG 3

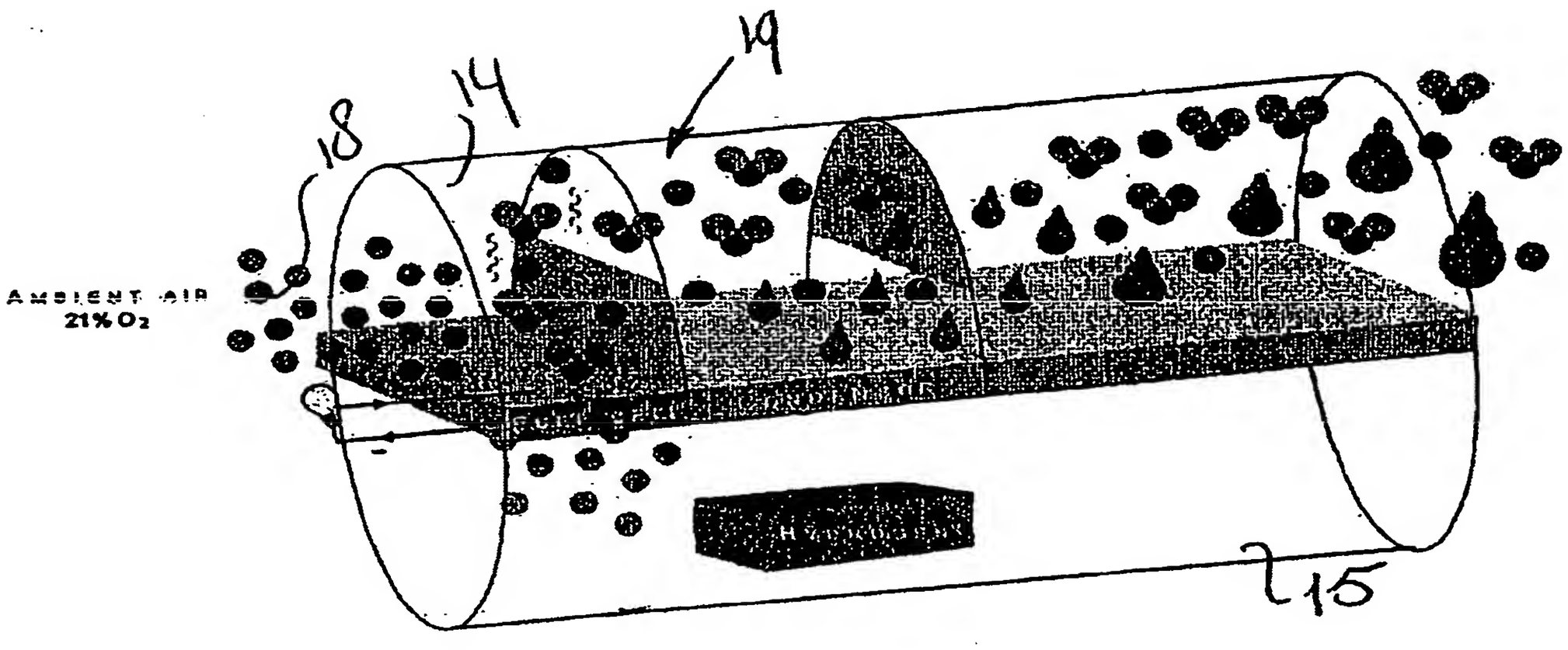


FIG 4

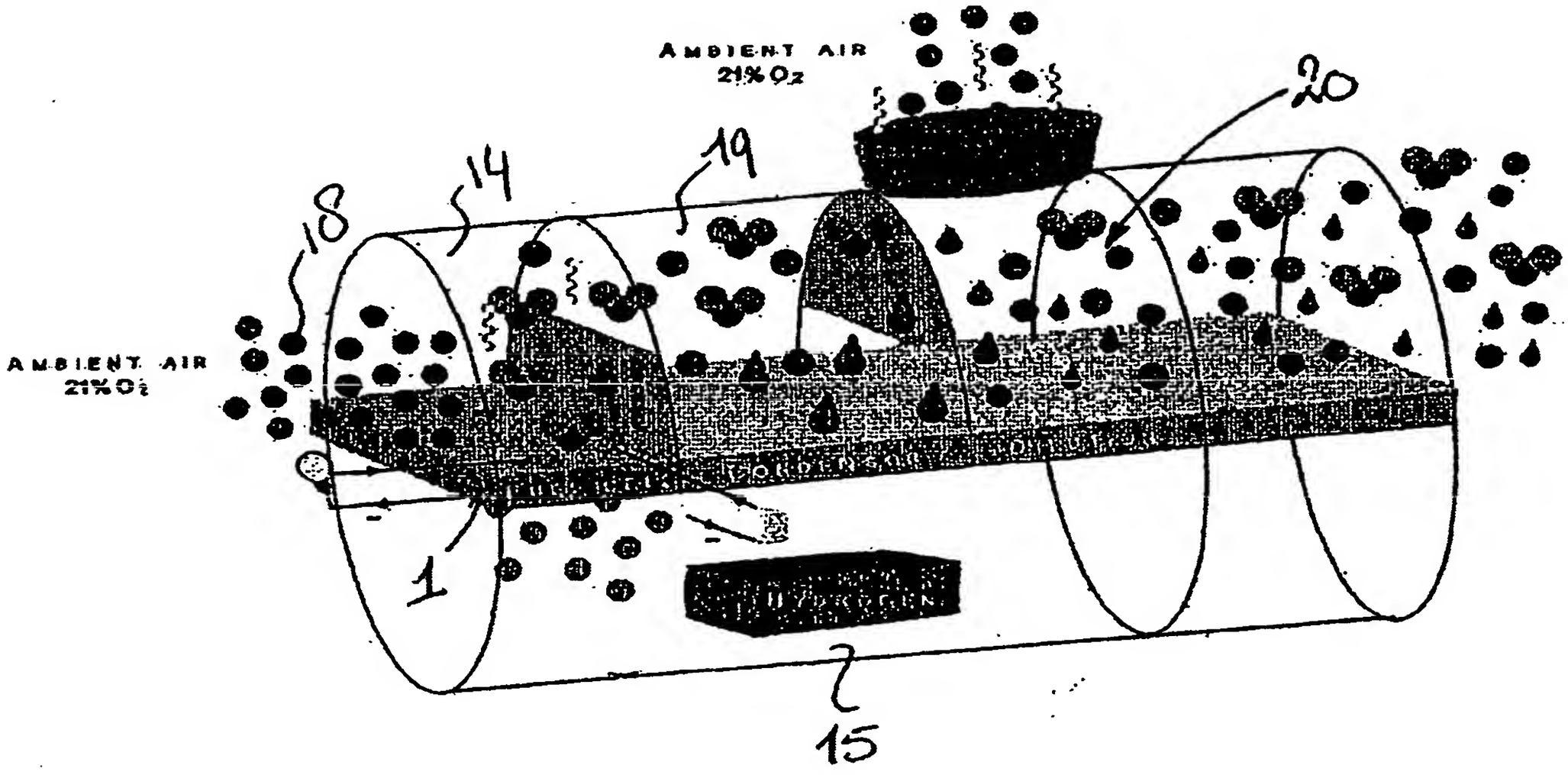


FIG 5

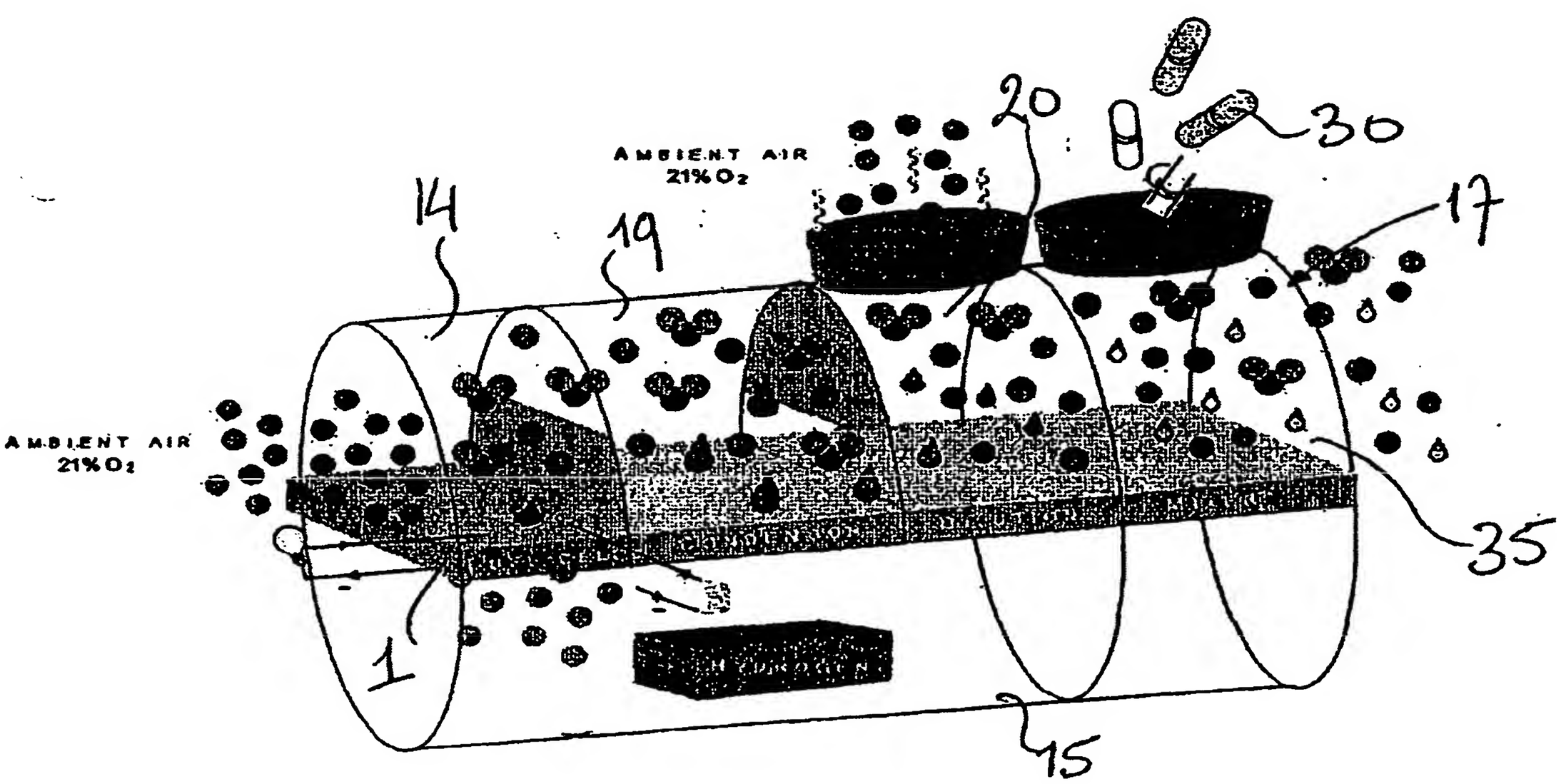


FIG 6

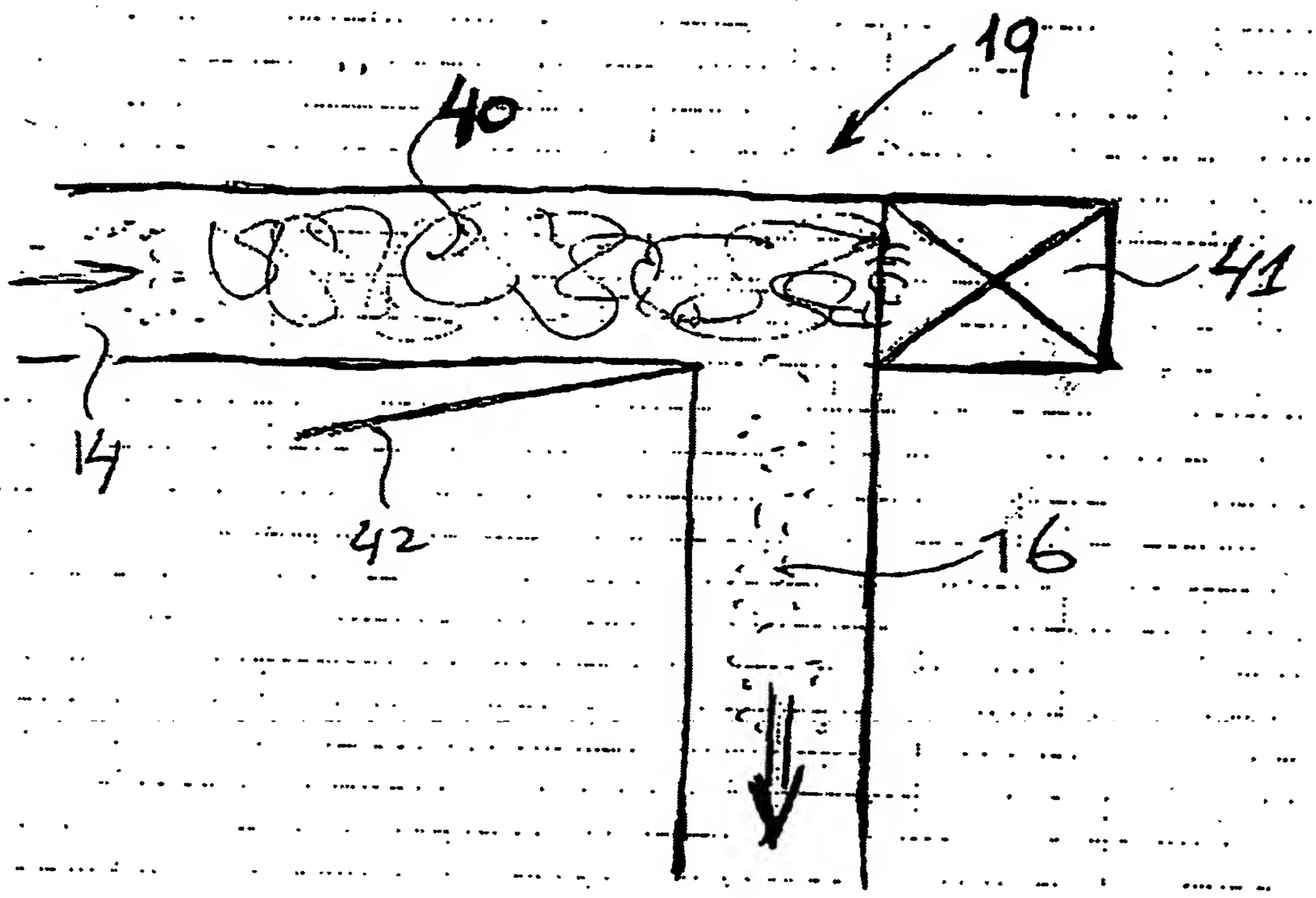


Fig 7

Koninkrijk der Nederlanden

OCTROOICENTRUM NEDERLAND

Hierbij wordt verklaard, dat in Nederland op 24 februari 2004 onder nummer 1025556,
ten name van:
Jacob KOREVAAR
te Haarlem
een aanvrage om octrooi werd ingediend voor:
"Device and method for administration of a fluid to a mammal",
en dat de hieraan gehechte stukken overeenstemmen met de oorspronkelijk ingediende stukken.

Rijswijk, 15 maart 2007

De Directeur van Octrooicentrum Nederland,
voor deze,

D.H. de Haas